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Attorney Docket No.: 022266-000940US

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

On July 22, 2004

TOWNSEND and TOWNSEND and CREW LLP

By: Mark T. Davis  
Mark T. Davis



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re application of:

Jordan J.N. Tang et al.

Application No.: 10/820,953

Filed: April 8, 2004

For: INHIBITORS OF MEMAP SIN 2  
AND USE THEREOF

Examiner: Not Yet Assigned

Art Unit: Not Yet Assigned

INFORMATION DISCLOSURE  
STATEMENT UNDER 37 CFR §1.97 and  
§1.98

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Sir:

The references cited on attached form PTO/SB/08B are being called to the attention of the Examiner. In accordance with 37 CFR §1.98(d), copies of the references can be found in Application No. 09/603,713, filed June 27, 2000 (Attorney Docket No. 022266-000910US). It is respectfully requested that the cited references be expressly considered during the prosecution of this application, and the references be made of record therein and appear among the "references cited" on any patent to issue therefrom.

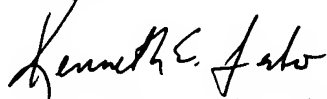
As provided for by 37 CFR 1.97(g) and (h), no inference should be made that the information and references cited are prior art merely because they are in this statement and no

representation is being made that a search has been conducted or that this statement encompasses all the possible relevant information.

Applicant believes that no fee is required for submission of this statement.

However, if a fee is required, the Commissioner is authorized to deduct such fee from the undersigned's Deposit Account No. 20-1430. Please deduct any additional fees from, or credit any overpayment to, the above-noted Deposit Account.

Respectfully submitted,



Kenneth E. Jenkins, Ph.D.  
Reg. No. 51,846

TOWNSEND and TOWNSEND and CREW LLP  
Two Embarcadero Center, Eighth Floor  
San Francisco, California 94111-3834  
Tel: 415-576-0200  
Fax: 415-576-0300  
KEJ:mtd  
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<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)			<b>Complete if Known</b>		
			Application Number	10/820,953	
			Filing Date	April 4, 2004	
			First Named Inventor	Jordan J.N. Tang	
			Art Unit	Not Yet Assigned	
			Examiner Name	Not Yet Assigned	
Sheet	3	of	Attorney Docket Number		022266-000940US

U.S. PATENT DOCUMENTS+					
Examiner Initials*	Cite No. <sup>1</sup>	Document Number	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number Kind Code <sup>2</sup> (if known)			
	AA	US-4,923,967	05/08/90	Bobbitt, et al.	
	AB	US-5,235,043	08/10/93	Collins, et al.	
	AC	US6,207,710 B1	03/27/01	Audia, et al.	
	AD	US-6,245,884 B1	06/12/01	Hook	
	AE	US-6,291,223 B1	09/18/01	Christie, et al.	
	AF	US-6,313,268 B1	11/06/01	Hook	
	AG	US-6,319,689 B1	11/20/01	Powell, et al.	
	AH	US-6,329,163 B1	12/11/01	Anderson, et al.	
	AI	US-6,361,975 B1	03/26/02	Christie, et al.	
	AJ	US-2002/0111365 A1	08/15/02	Wolfe, et al.	
	AK	US-2002/0157122 A1	10/24/02	Wong, et al.	
	AL	US-2002/0159991 A1	10/31/02	Cordell, et al.	

FOREIGN PATENT DOCUMENTS								
Examiner Initials*	Cite No. <sup>1</sup>	Foreign Patent Document			Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
		Country Code <sup>3</sup>	Number <sup>4</sup>	Kind Code <sup>5</sup> (if known)				
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	BF	JP	10108681	A	04/28/88			<input type="checkbox"/>

Examiner Signature		Date Considered	
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Sheet	4	of	Attorney Docket Number	022266-000940US

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	BG	ABAD-ZAPATERO, et al., "Structure of a secreted aspartic protease from <i>C. albicans</i> complexed with a potent inhibitor: implications for the design of antifungal agents," <i>Protein Sci</i> 5(4):640-52 (1996).	
	BH	ABBENATE, et al., "Inhibitors of $\beta$ -amyloid formation based on the $\beta$ -secretase cleavage site," <i>Biochemical and Biophysical Research Communications</i> 268(1):133-135 (2000).	
	BI	ASKEW, et al., "Molecular recognition with convergent functional groups. Synthetic and structural studies with a model receptor for nucleic acid components," <i>J. Am. Chem. Soc.</i> 111:1082-1090 (1989).	
	BJ	BAILEY & COOPER, "A structural comparison of 21 inhibitor complexes of the aspartic proteinase from <i>Endothia parasitica</i> ," <i>Protein Sci</i> 3(11):2129-43 (1994).	
	BK	BRUNGER, et al., "Crystallography & NMR system: A new software suite for macromolecular structure determination," <i>Acta Crystallogr D Biol Crystallogr</i> 54 ( Pt 5):905-21 (1998).	
	BL	CAPELL, et al., "The proteolytic fragments of the Alzheimer's disease-associated presenilin-1 form heterodimers and occur as a 100-150-kDa molecular mass complex," <i>J Biol Chem</i> 273(6):3205-11 (1998).	
	BM	CHARTIER-HARLIN, et al., "Early-onset Alzheimer's disease caused by mutations at codon 717 of the beta-amyloid precursor protein gene," <i>Nature</i> 353(6347):844-6 (1991).	
	BN	CITRON, et al., "Mutation of the beta-amyloid precursor protein in familial Alzheimer's disease increases beta-protein production," <i>Nature</i> 360(6405):672-4 (1992).	
	BO	COHEN, et al., "An artificial cell-cycle inhibitor isolated from a combinatorial library," <i>Proc Natl Acad Sci USA</i> 95(24):14272-7 (1998).	
	BP	CORDER, et al., "Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's DISEASE in late onset families," <i>Science</i> 261(5123):921-3 (1993).	
	BQ	COWLEY, et al., "Alzheimer's unlocking the mystery," <i>Newsweek</i> January 31, 2000.	
	BR	CUTFIELD, et al., "The crystal structure of a major secreted aspartic proteinase from <i>Candida albicans</i> in complexes with two inhibitors," <i>Structure</i> 3(11):1261-71 (1995).	
	BS	DAVIES, "The structure and function of the aspartic proteinases," <i>Annu Rev Biophys Chem</i> 9:189-215 (1990).	
	BT	DEALWIS, et al., "X-ray analysis at 2.0 Å resolution of mouse submaxillary renin complexed with a decapeptide inhibitor CH-66, based on the 4-16 fragment of rat angiotensinogen," <i>J. Mol. Biol.</i> 236(1):342-60 (1994).	
	BU	DE STROOPER, et al., "Deficiency of presenilin-1 inhibits the normal cleavage of amyloid precursor protein," <i>Nature</i> 391(6665):387-90 (1998).	
	BV	DORRELL, S. "Untangling Alzheimer's Disease with $\beta$ -secretase inhibitors," <i>Drug Discovery Today</i> , 5(8):316-317 (2000).	

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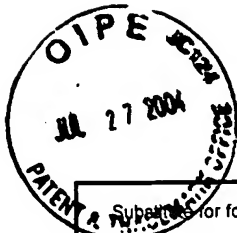
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Sheet	5	of	Attorney Docket Number 022266-000940US	

NON PATENT LITERATURE DOCUMENTS				
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	BW	DUNN, Structure and Functions of the Aspartic Proteinases, Adv. in Exptl. Med. Biol. 306 (Plenum Press, NY 1991).		
	BX	ELLINGTON & SZOSTAK, "In vitro selection of RNA molecules that bind specific ligands," <i>Nature</i> 346(6287):818-22 (1990).		
	BY	ERMOLIEFF et al., "Proteolytic activation of recombinant Pro-memapsin 2 (Pro- $\beta$ -secretase) studied, with new fluorogenic substrates," <i>Biochemistry</i> 39(40):12450-12456 (2000).		
	BZ	FAN, et al., "BACE Maps to chromosome 11 and a BACE homolog, BACE2, reside in the obligate down syndrome region of chromosome 21," <i>Science</i> 286:1255a (1999).		
	CA	FIELDS & SONG, "A novel genetic system to detect protein-protein interactions," <i>Nature</i> 340(6230):245-6 (1989).		
	CB	GHOSH & FIDANZE, Transition-state mimetics for HIV protease inhibitors: Stereocontrolled synthesis of hydroxyethylene and hydroxyethylamine isosteres by ester-derived titanium enolate syn and anti-aldol reactions," <i>Org. Chem.</i> 63:6146-54 (1998).		
	CC	GHOSH, A.K. et al., "Structure-Based Design: Potent Inhibitors of Human Brain Memapsin 2 ( $\beta$ -Secretase)," <i>J. Med. Chem.</i> 44:2865-2868 (2001).		
	CD	GHOSH et al., "Design of potent inhibitors for human brain memapsin 2 ( $\beta$ -secretase)," <i>J. Am Chem Soc</i> 122(14):3522-3523 (2000).		
	CE	GLENNER & WONG, "Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein," <i>Biochem Biophys Res Commun</i> 120(3):885-90 (1984).		
	CF	GOATE, et al., "Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease," <i>Nature</i> 349(6311):704-6 (1991).		
	CG	GOLDGABER, et al., "Characterization and chromosomal localization of a cDNA encoding brain amyloid of Alzheimer's disease," <i>Science</i> 235(4791):877-80 (1987).		
	CH	GURNEY, M.E. et al., "U.S. Published Patent Application, US 2002/0037315 A1," published Mar. 28, 2002, filing date Feb. 27, 2001.		
	CI	HAASS & DE STROOPER, "The presenilins in Alzheimer's disease--Proteolysis holds the key," <i>Science</i> 286:916-919 (1999).		
	CJ	HONG et al., "Structure of the protease domain of memapsin. 2 ( $\beta$ -secretase) complexed with inhibitor," <i>Science</i> 290:150-153 (2000).		
	CK	HOWLETT, D.R. et al., "In search of an enzyme: the $\beta$ -secretase of Alzheimer's disease is an aspartic proteinase," <i>Trends Neurosci.</i> 23:565-570 (2000).		
	CL	JAMES, Aspartic Proteinases, Retroviral and Cellular Enzymes, Adv. in Exptl. Med. Biol. 436 (Plenum Press, NY 1998).		

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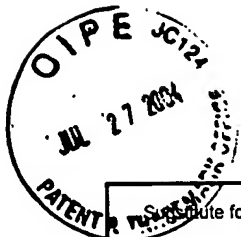
Substitutes for form 1449B/PTO <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b> (use as many sheets as necessary)		<b>Complete if Known</b>	
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Sheet	6	of	

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	CM	JONES, et al., "Improved methods for binding protein models in electron density maps and the location of errors in these models" <i>Acta Crystallogr A</i> 47 ( Pt 2):110-9 (1991).	
	CN	JORM, ed., <i>A Guide to the Understanding of Alzheimer's Disease and Related Disorders</i> (New York University Press, New York 1987).	
	CO	KANG, et al., "The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor," <i>Nature</i> 325(6106):733-6 (1987).	
	CP	KEARNEY & AWEEKA, "The penetration of anti-infectives into the central nervous system," <i>Neurol. Clin.</i> 17(4):883-900 (1999).	
	CQ	KELLY & DOW, "Microbial differentiation: the role of cellular asymmetry," <i>Microbiol Sci</i> 1:214-9 (1984).	
	CR	KHAN, et al., "Lowering the entropic barrier for binding conformationally flexible inhibitors to enzymes," <i>Biochemistry</i> 37(48):16839-45 (1998).	
	CS	KNOPS, et al., "Cell-type and amyloid precursor protein-type specific inhibition of A beta release by bafilomycin A1, a selective inhibitor of vacuolar ATPases," <i>J Biol Chem</i> 270(6):2419-22 (1995).	
	CT	KOLATA, "Scientists find enzyme linked to Alzheimer's," <i>National Science/Health</i> October 22, 1999.	
	CU	KOSTKA, <i>Aspartic proteinases and Their Inhibitor</i> (Walter de Gruyter, Berlin 1985).	
	CV	LASKOWSKI, et al., "Procheck: a program to check the stereochemical quality of protein structures," <i>J Appl. Crystallog</i> 26:283 (1993).	
	CW	LEMAIRE, et al., "The PreA4(695) precursor protein of Alzheimer's disease A4 amyloid is encoded by 16 exons," <i>Nucleic Acids Res</i> 17(2):517-22 (1989).	
	CX	LEVY et al., "Mutation of the Alzheimer's disease amyloid gene in hereditary cerebral hemorrhage, Dutch type," <i>Science</i> 248(4959):1124-6 (1990).	
	CY	LEVY-LAHAD, et al., "Candidate gene for the chromosome 1 familial Alzheimer's disease locus," <i>Science</i> 269(5226):973-7 (1995).	
	CZ	LEWIS & DEAN, "Automated site-directed drug design: the concept of spacer skeletons for primary structure generation," <i>Proc R Soc Lond B Biol Sci</i> 236(1283):125-40 and 141-162 (1989).	
	DA	LIN, et al., "Intracellular diversion of glycoprotein GP 160 of human immunodeficiency virus to lysosomes as a strategy of AIDS gene therapy," <i>FASEB J</i> 7(11):1070-80 (1993).	
	DB	LIN et al., "Human aspartic protease memapsin 2 cleaves the beta-secretase site of beta-amyloid precursor protein," <i>PNAS</i> 97(4):1456-1460 (2000).	

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	DC	MAJER, P. et al., "Structure-based subsite specificity mapping of human cathepsin D using statine-based inhibitors," <i>Protein Science</i> , 6(7):1458-1466 (1977).		
	DD	MANN, "Cerebral amyloidosis, ageing and Alzheimer's disease; a contribution from studies on Down's syndrome," <i>Neurobiol Aging</i> 10(5):397-9 (1989).		
	DE	MARCINISZYN, et al., "Mode of inhibition of acid proteases by pepstatin," <i>J Biol. Chem.</i> 251(22):7088-94 (1976).		
	DF	MARTSON, F.A.O. et al., "Solubilization of protein aggregates," <i>Methods of Enzymology</i> , 182:264-276 (1990).		
	DG	MATSUMOTO, et al., "Molecular cloning of human cDNA with a sequence highly similar to that of the dihydrofolate reductase gene in brain libraries derived from Alzheimer's patients," <i>Eur. J. Biochem.</i> 230:337-343 (1995).		
	DH	MECKELEIN, et al., "Identification of a novel serine protease-like molecule in human brain," <i>Molecular Brain Research</i> 55:181-197 (1998).		
	DI	MCKINLAY & ROSSMANN, "Rational design of antiviral agents," <i>Annu Rev Pharmacol Toxicol</i> 29:111-22 (1989).		
	DJ	MULLAN, et al., "A locus for familial early-onset Alzheimer's disease on the long arm of chromosome 14, proximal to the alpha 1-antichymotrypsin gene," <i>Nat Genet</i> 2(4):340-2 (1992).		
	DK	MULLAN, et al., "A pathogenic mutation for probable Alzheimer's disease in the APP gene at the N-terminus of beta-amyloid," <i>Nat Genet</i> 1(5):345-7 (1992).		
	DL	MURRELL, et al., "A mutation in the amyloid precursor protein associated with hereditary Alzheimer's disease," <i>Science</i> 254(5028):97-9 (1991).		
	DM	NAVAZA, "AMoRe: an automated package for molecular replacement," <i>Acta Crystallog Sect A</i> 50:157 (1997).		
	DN	OEFNER, C. et al., "Renin inhibition by substituted piperidines: A novel paradigm for the inhibition of monomeric aspartic proteinases?" <i>Chemistry &amp; Biology (London)</i> , 6(3):127-131 (1999).		
	DO	OTWINOWSKI & MINOR, "Processing of X-ray diffraction data collected in Oscillation mode," <i>Methods Enzymol</i> 276:307 (1997).		
		PARIS, N. et al., "Bacterial Production and Purification of Recombinant Human Prolactin," <i>Biotechnology and Applied Biochemistry</i> , 12:436-449 (1990).		
	DP	PEREZ, et al., "Enhanced release of amyloid beta-protein from codon 670/671 "Swedish" mutant beta-amyloid precursor protein occurs in both secretory and endocytic pathways," <i>J Biol Chem</i> 271(15):9100-7 (1996).		
	DQ	PERRY & DAVIES, <u>QSAR: Quantitative Structure-Activity Relationships in Drug Design</u> pp. 189-193 (Alan R. Liss, Inc. 1989).		

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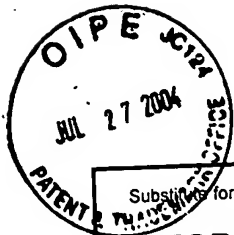
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	DR	PHIMISTER, "Four companies announce discovery of b-secretase gene," <i>Nature Biotechnology</i> 18:16 (2000).	
	DS	PODLISNY, et al., "Presenilin proteins undergo heterogeneous endoproteolysis between Thr291 and A1a299 and occur as stable N- and C-terminal fragments in normal and Alzheimer brain tissue," <i>Neurobiol Dis</i> 3(4):325-37 (1997).	
	DT	RIPKA, "Computers picture the perfect drug," <i>New Scientist</i> 54-57 (1988).	
	DU	ROBAKIS, et al., "Molecular cloning and characterization of a cDNA encoding the cerebrovascular and the neuritic plaque amyloid peptides," <i>Proc Natl Acad Sci U S A</i> 84(12):4190-4 (1987).	
	DV	ROBERTS & SZOSTAK, "RNA-peptide fusions for the in vitro selection of peptides and proteins," <i>Proc Natl Acad Sci U S A</i> 94(23):12297-302 (1997).	
	DW	ROGAEV, et al., "Familial Alzheimer's disease in kindreds with missense mutations in a gene on a chromosome 1 related to the Alzheimer's disease type 3 gene," <i>Nature</i> 376(6543):775-8 (1995).	
	DX	ROTELLA, D.P. "Fenchylamine Sulfonamide Inhibitors of Amyloid $\beta$ -Peptide Production by the $\gamma$ -Secretase Proteolytic Pathway: Potential Small Molecule Therapeutic Agents for the Treatment of Alzheimer's Disease," <i>Chemtracts - Organic Chemistry</i> 13:626-629 (2000).	
	DY	ROUVINEN, et al., "Computer aided drug design," <i>Acta Pharmaceutica Fennica</i> 97, 159-166 (1988).	
	DZ	RUMBLE, et al., "Amyloid A4 protein and its precursor in Down's syndrome and Alzheimer's disease," <i>N Engl J Med</i> 320(22):1446-52 (1989).	
	EA	SELKOE, et al., "Translating cell biology into therapeutic advances in Alzheimer's disease," <i>Nature</i> 399(6738 Suppl):A23-31 (1999).	
	EB	SHERRINGTON, et al., "Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease," <i>Nature</i> 375(6534):754-60 (1995).	
	EC	SINHA & LIEBERBURG, "Cellular mechanisms of beta-amyloid production and secretion," <i>Proc Natl Acad Sci U S A</i> 96(20):11049-53 (1999).	
	ED	SINHA, et al., "Purification and cloning of amyloid precursor protein beta-secretase from human brain," <i>Nature</i> 402(6761):537-40 (1999).	
	EE	STEINER, et al., "Expression of Alzheimer's disease-associated presenilin-1 is controlled by proteolytic degradation and complex formation," <i>J Biol Chem</i> 273(48):32322-31 (1998).	
	EF	SUZUKI, et al., "An increased percentage of long amyloid beta protein secreted by familial amyloid beta protein precursor (beta APP717) mutants," <i>Science</i> 264(5163):1336-40	
	EG	SYMERSKY, et al., "High-resolution structure of the extracellular aspartic proteinase from <i>Candida tropicalis</i> yeast," <i>Biochemistry</i> 36(42):12700-10 (1997).	

Examiner Signature	Date Considered
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\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

<sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> Applicant is to place a check mark here if English language Translation is attached.





Substitution for form 1449B/PTO		<b>Complete if Known</b>	
<b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  (use as many sheets as necessary)		Application Number	10/820,953
		Filing Date	April 4, 2004
		First Named Inventor	Jordan J.N. Tang
		Art Unit	Not Yet Assigned
		Examiner Name	Not Yet Assigned
		Attorney Docket Number	022266-000940US
Sheet	9	of	

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials *	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
	EH	SZOSTAK, "In vitro genetics," <i>TIBS</i> 19:89 (1992).	
	EI	TAGAWA, et al., "Alzheimer's disease amyloid $\beta$ -clipping enzyme (APP secretase): Identification, purification, and characterization of the enzyme," <i>Biochemical and Biophysical Research Communications</i> 177(1):377-387 (1991).	
	EJ	TAKAHASHI, Aspartic Proteases, Structure, Function, Biology, Biomedical Implications, Adv. in Exptl. Med. Biol. 362 (Plenum Press, NY 1995).	
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	EM	TANZI, et al., "Protease inhibitor domain encoded by an amyloid protein precursor mRNA associated with Alzheimer's disease," <i>Nature</i> 331(6156):528-30 (1988).	
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	EO	THINAKARAN, et al., "Endoproteolysis of presenilin 1 and accumulation of processed derivatives in vivo," <i>Neuron</i> 17(1):181-90 (1996).	
	EP	THINAKARAN, et al., "Evidence that levels of presenilins (PS1 and PS2) are coordinately regulated by competition for limiting cellular factors," <i>J Biol Chem</i> 272(45):28415-22 (1997).	
	EQ	THINAKARAN, et al., "Stable association of presenilin derivatives and absence of presenilin interactions with APP," <i>Neurobiol Dis</i> 4(6):438-53 (1998).	
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	ES	VAN BROECKHOVEN, et al., "Amyloid beta protein precursor gene and hereditary cerebral hemorrhage with amyloidosis (Dutch)," <i>Science</i> 248(4959):1120-2 (1990).	
	ET	VASSAR, et al., "Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE," <i>Science</i> 286(5440):735-41 (1999).	
	EU	WOLFE, et al., "Two transmembrane aspartates in presenilin-1 required for presenilin endoproteolysis and gamma-secretase activity," <i>Nature</i> 398(6727):513-7 (1999).	
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	EW	YOSHIKAI, et al., "Genomic organization of the human amyloid beta-protein precursor gene," <i>Gene</i> 87(2):257-63 (1990).	

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**INFORMATION DISCLOSURE  
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Sheet

10

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	EX	YU, "Inhibition of beta-amyloid cytotoxicity by midkine," <i>Neurosci Lett</i> 254(3):125-8 (1998).	

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